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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,477	06/07/2005	Chih-Chang Chu	CHUC3007	2280

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EXAMINER	
HAIDER, SAIRA BANO	
ART UNIT	PAPER NUMBER
1796	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,477	CHU ET AL.	
	Examiner	Art Unit	
	SAIRA HAIDER	1796	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ekman et al. (US 4,822,535) in view of Moiser (US 4,492,720), Hatsuda (US 6,194,531), and Cruise (Biomaterials).

3. Ekman discloses method of producing small spherical polymer particles from systems containing two liquid phases, the one phase of which contains one or more dissolved substances and is dispersed in the form of small droplets in the other phase to form an emulsion, whereafter the droplets are converted to a solid form. The liquid phases used are two mutually immiscible aqueous phases (abstract). Ekman notes that whole (living) cells, cell organelles, solid particles or small oil droplets can be encapsulated when practicing the invention (col. 8, lines 15-17).

4. In example 6, Ekman discloses the preparation of spherical particles of cross-liked dextran. The process involves preparing a first aqueous solution of acryldextran (M_w=40,000). Ekman discloses that acryldextran which functions as both the monomer and a crosslinker. Next, a second aqueous solution is then prepared from polyethylene glycol (M_w=6,000). The first aqueous solution is added to the second aqueous solution and emulsified, wherein the first aqueous solution is the inner phase (the droplets). Polymerization is initiated via a catalyst. The particles are collected via filtration.

5. Ekman fails to explicitly disclose the size of the droplets; however Ekman notes that the particle size of the solid particles obtained can be controlled in all of the disclosed embodiments in a manner known per se, for example by stirring with varying intensities or by selecting suitable

viscosities for the various phases. In the case of the system polyethylene glycol-starch the particle size can also be regulated by selection of the molecular weight of the polyethylene glycol, a polyethylene glycol of higher molecular weight providing larger particles (col. 7, lines 66 to col. 8, lines 4). Thus attention is directed to the Moiser reference, which discloses a method of preparing microspheres for intravascular delivery. Specifically, Moiser creates the microspheres via formation of an emulsion of two phases, wherein the droplets that comprise the dispersed phase have average sizes in the range of 50-150 microns (col. 4, lines 3-26). Wherein the resulting microspheres are in the range of 50-350 microns and are rendered suitable for administration of therapeutic agents and diagnostic agents via intra-arterial delivery (col. 1, lines 49-59). Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the invention to alter the Ekman process conditions (as taught by Ekman) in order to form droplets and resulting microcapsules suitable for intra-arterial delivery, as taught by Moiser.

6. Ekman applies as above and notes that polyethylene glycol is preferably the continuous phase (col. 3, lines 19-24); however Ekman discloses that suitable two-phase systems of polymeric aqueous solutions include dextran/polyethylene glycol/water and polyethylene glycol/dextran sulphate/water (col. 1, line 66 to col. 2, line 19). Accordingly, it is readily envisaged that polyethylene glycol is the dispersed phase and dextran is the continuous phase.

7. It is noted that Ekman discloses polyethylene glycol as the dispersed phase, but fails to disclose the claimed polyethylene glycol diacrylate monomer, as claimed. Thus attention is directed to the Hatusda reference, which discloses the use of polyethylene glycol diacrylate (PEGDA) monomers as a crosslinking agent in the formation of hydrogels particulates (col. 19, lines 28-63). Wherein it would have been obvious to one of ordinary skill in the art to include the crosslinking PEGDA monomers of Hatusda in the microcapsule emulsion of Ekman and Moiser in order to

improve the strength of the microcapsule via crosslinking and thereby increase the sustained release of the core material.

8. The Hatsuda reference fails to disclose the claimed PEG molecular weight of the PEGDA, thus attention is directed to the Cruise reference which discloses PEGDA with a PEG precursor having molecular weights in the range of 2K to 20K. Cruise discloses that selection of the PEG molecular weight for the PEGDA results in different protein impermeabilities. For example PEGDA formed using a PEG having a molecular weight of 2K, 4K, or 8K resulted in a hydrogel impermeable to proteins larger than 22kDa (such as myoglobin), and PEGDA formed using a PEG having a molecular weight of 20K resulted in a hydrogel impermeable to proteins larger than 45kDa (such as ovalbumin) (abstract). Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to control the molecular weight of the PEG precursor of PEGDA in order to ensure impermeability of certain sized protein molecules.

9. The PEG molecular weight of PEGDA is recognized as a result-effective variable because changing it will clearly affect the type of product obtained. Wherein an increase in the PEG molecular weight to 20K will result in a hydrogel impermeable to proteins larger than 45kDa. Thus it would have been obvious to one of ordinary skill in the art to utilize a PEGDA having a PEG of 20K in order to ensure impermeability of proteins such as ovalbumin.

10. Claims 3-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekman et al. (US 4,822,535) in view of Moiser (US 4,492,720), Hatsuda (US 6,194,531), and Cruise (Biomaterials), and in further view of Nelson (US 6,596,296).

11. In reference to claims 3-4, Ekman applies as above but fails to disclose the claimed second hydrogel precursor as N-isopropylacrylamide. Thus attention is directed to the Nelson reference,

which discloses drug releasing biodegradable fiber implants. Specifically, Nelson discloses polymer hydrogel nanospheres loaded with biological molecules, wherein useful polymer hydrogels include N-isopropylacrylamide (NIPA). Nelson recognizes NIPA gels as having the ability to undergo dramatic volume changes of 100 fold in response to small (2-3°C) temperature change; specifically, the phase transition can be adjusted to occurs at 38-39 °C such that the nanosphere is responsive to the physiological state of the patient. The nanospheres release the drug in response to an increase in the body temperature of a patient. (Example 4 at col. 20, line 40-67). Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the invention to include NIPA in the polymer hydrogel taught by Ekman, Moiser, Hatsuda, and Cruise above in order to form a composition which readily releases the active core component upon a temperature change.

12. In reference to claims 5-7, it is noted that Ekman discloses these limitations. Specifically, Ekman discloses dextran as a suitable continuous phase and Ekman exemplifies utilization of dextran with M_w of 40,000 (Example 6). Further, Ekman discloses the inclusion of water soluble salts such as magnesium sulphate which will reduce the solubility of dextran in the water (col. 2, lines 21-36). Wherein utilization of such disclosure of Ekman in the invention taught by the combination of references would be obvious to one of ordinary skill in the art.

Response to Arguments

13. Applicant's arguments filed 10/20/2009 have been fully considered but they are not persuasive.

14. Applicant has essentially argued that Example 6 of Ekman, relied on in the rejection, is irrelevant. In response, Example 6 is relied because it teaches the claimed process, specifically, forming a first aqueous solution, admixing the first aqueous solution with a second aqueous solution, forming an emulsion, polymerization to form hydrogel microspheres and collection of the

microspheres. As noted in the rejection Ekman notes that polyethylene glycol is preferably the continuous phase, however Ekman discloses that polyethylene glycol can function as the dispersed phase. Specifically Ekman discloses that aqueous two-phase systems comprises at least one polymer dissolved therein, Ekman then exemplifies dextran/polyethylene glycol/water and polyethylene glycol/dextran sulphate/water (col. 1, line 66 to col. 2, line 19). Thus it is clear that in one embodiment Ekman discloses dextran as the disperse phase and polyethylene glycol as the continuous phase (as exemplified in Example 6) and alternatively dextran as the continuous phase and polyethylene glycol as the dispersed phase.

15. Applicant then argues that polyethylene glycol diacrylate as claimed is chemically different from polyethylene glycol /dextran. The examiner recognizes that the claimed polyethylene glycol diacrylate is distinct from polyethylene glycol, hence reliance on the Hatsuda reference. Hatsuda teaches that the claimed polyethylene glycol diacrylate functions as a crosslinker (col. 19, lines 28-63). Wherein it would have been obvious to one skilled in the art to include PEGDA as a crosslinker in the dispersed phase (polyethylene glycol phase) of the hydrogel microcapsule formation process of Ekman in order to strengthen the microcapsule shell and this increase the sustained release of the core material. Applicants note that Hatsuda is drawn to hydrogel particulates and thus it would not have been obvious to use PEGDA to form microcapsules. In response, the fact that Hatsuda forms particulate hydrogels does not distract from Hatsuda's teaching of PEGDA as a suitable crosslinker for hydrogels. Hatsuda's PEGDA teaching is relied on in the rejection to crosslink the microcapsule emulsion of Ekman, not to solely form a microcapsule from PEGDA.

16. Only a reasonable expectation of success, not absolute predictability is necessary for obviousness. *In re Longi,* 759F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985). An expectation

is reasonable if one of ordinary skill in the art would have considered it "logical to anticipated with a high degree of probability that a trial of the combination would have been successful." *In re Pantzer,* 341 F2d. 121, 126;144 USPQ 415, 419 (CCPA 1965).

17. There is a reasonable expectation of success because the PEGDA of Hatsuda functions to crosslink a hydrogel, wherein Ekman discloses formation of a hydrogel. Thus one of ordinary skill would have considered it logical that the combination the PEGDA to crosslink the hydrogel of Ekman would have been successful.

18. It is noted that PEGDA reads on the claimed hydrogel precursor of the first aqueous solution, since it functions to crosslink the microcapsule in the dispersed phase of Ekman. In reference to the hydrogel precursor functioning as both a crosslinking and a monomer in hydrogel formation, attention is directed to MPEP § 2112, which states "products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, since the combination of the prior art references teach the identical chemical structures, PEGDA, the properties applicant discloses and/or claims (monomer in hydrogel formation) are necessarily present.. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The burden shifts to the applicant to show an unobvious difference. Note that because the reference does not expressly teach or address the properties of the claimed invention, does not mean that the properties are not inherently disclosed. Teaching the same compound(s) inherently discloses the corresponding properties. The references cannot possibly teach or address all of the properties, but implicitly all of the properties are present.

19. Applicant argues that Nelson fails to disclose nanospheres and fails to provide any suggestion to combine PEGDA with NIPA to form micro/nanospheres. In response, attention is directed to Example 4 of Nelson (col. 20, lines 40-67) which explicitly discloses the formation of

polymer hydrogels in nanospheres size, wherein suitable polymer hydrogels include NIPA, and can be loaded with biological molecules via soaking in an aqueous solution of the biomolecules. Furthermore, Nelson notes that NIPA nanosphere hydrogels release the active component upon a temperature change.

20. Only a reasonable expectation of success, not absolute predictability is necessary for obviousness. *In re Longi,* 759F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985). An expectation is reasonable if one of ordinary skill in the art would have considered it "logical to anticipated with a high degree of probability that a trial of the combination would have been successful." *In re Pantzer,* 341 F2d. 121, 126;144 USPQ 415, 419 (CCPA 1965).

21. There is a reasonable expectation of success because the NIPA of Nelson functions to form a nanosphere hydrogel, wherein Ekman discloses formation of a microcapsule hydrogel and Hatsuda discloses a hydrogel crosslinker. Thus one of ordinary skill would have considered it logical that the combination the NIPA to form the microcapsule hydrogel taught by Ekman and Hatsuda would have been successful.

Conclusion

22. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAIRA HAIDER whose telephone number is (571)272-3553. The examiner can normally be reached on Monday-Friday from 10am-6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Seidleck can be reached on (571) 272-1078. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James J. Seidleck/
Supervisory Patent Examiner, Art Unit 1796

Saira Haider
Examiner
Art Unit 1796

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